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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,174	11/17/2003	Quan Nguyen	70-000150US	3901

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EXAMINER	
YU, MELANIE J	
ART UNIT	**PAPER NUMBER**
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,174	NGUYEN ET AL.	
	Examiner	Art Unit	
	Melanie Yu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13-19,21-56,59-61 and 201-221* is/are pending in the application.

4a) Of the above claim(s) *14-17 and 201-221* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13,18,19,21-56 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/14*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's after final amendment filed 14 December 2006 has been entered.

Withdrawn Rejections

2. Applicant's amendments and arguments have overcome previous rejections under 35 USC 112, second paragraph, 35 USC 102(b) and 35 USC 103(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 21-46 and 59-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 29, 36 and 45 recite "1) a cell comprising an enzyme and a caged sensor" and "2) an enzyme and a caged sensor". It is unclear whether the composition is intended to claim (1) a cell comprising a first enzyme and caged sensor and a separate enzyme and caged sensor outside of the cell, (2) the claim is referring to the same enzyme and caged sensor or (3) more than one enzyme and more than one caged sensor are present inside the cell.

4. Claims 27, 34 and 43 recites the limitation "the second caging groups" in the first line of the claims. There is insufficient antecedent basis for this limitation in the claim. It is further unclear how the second caging groups are related to the composition and whether they are present on the substrate.

5. With respect to claims 59 and 60 it is unclear whether the matrix that the second oligonucleotide is part of the composition and whether the caged sensor actually comprises the matrix since the second oligonucleotide is not actually attached to the first oligonucleotide. It is vague as to whether the composition must comprise the second

oligonucleotide and the matrix to which it is bound, whether the second oligonucleotide is actually part of the caged sensor and is within the cell or whether the caged sensor is merely attached to a first oligonucleotide that is capable of binding to a second oligonucleotide which is bound to a matrix and the matrix is not actually required for the composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1, 6, 9, 10, 18, 21, 23-25 and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ting et al. (Genetically encoded fluorescent reporters of protein tyrosine kinase activities in living cells, 2001, PNAS, Vol. 98, no. 26, pages 15003-15008) in view of Burbaum et al. (US 5,981,207) further in view of Walker et al. (Signaling pathways underlying eosinophil cell motility revealed by using caged peptides, 1998, PNAS, pg 1568-1573).

Ting et al. teach a composition comprising: a cell (characterization in mammalian cells, pg. 15003, right column, second paragraph): an enzyme (kinase activity is detected in

the cell, therefore the enzyme is in the cell, pg. 15005, right column, cellular response of the Src Reporter) and a sensor, wherein the sensor comprises: a substrate for the enzyme wherein the substrate is in a first state on which the enzyme can act, thereby converting the substrate to a second state (substrate undergoes significant conformational change, pg. 15003, left column, first paragraph), and a first label, wherein a first signal is exhibited by the first label when the substrate is in its first state and is distinguishable from a second signal exhibited by the first label when the substrate is in its second state (pg. 15003, left column, last paragraph-right column, first paragraph). Ting et al. fail to teach one or more first caging groups associated with the one or more molecules.

Burbaum et al. teach a caged enzyme substrate placed into a cell (col. 7, lines 36-47), in order to release the substrate into an activated for at an appropriate time.

Walker et al. teach a caged peptide to provide rapid detection results with good spatial resolution (pg. 1568, right column-left column, first paragraph.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the composition of Ting et al., the substrate being caged as taught by Burbaum et al., in order to provide injection into a cell and give time to allow the substrate to distribute evenly so normal cell activity can be detected.

With respect to claim 6, Ting et al. also teach the label being an optically detectable label and the second signal being a fluorescent signal that has a greater intensity than the first signal (FRET change creates fluorescent signal after conformational change and reverses the FRET change prior to conformational change (pg. 15003, left column, last paragraph-right column, first paragraph).

Regarding claims 3-5, the claims are drawn to intended use of a composition and do not appear to require any further physical limitations. Therefore, since all physical limitations required for the composition as recited in claim 1 are taught by Ting et al. in

view of Burbaum et al. further in view of Walker et al., as described above, the composition of Ting et al. in view of Burbaum et al. further in view of Walker is capable of providing the uses recited in claims 3-5.

With respect to claims 7-8, Burbaum et al. teach the caging groups being covalently attached to the enzyme substrate, wherein the caging groups are photoliabile and are removed by exposure to light of 366 nm (col. 22, lines 40-55), which is encompassed by the range of between about 60 nm and about 400 nm.

Regarding claims 9, 10 and 18, Ting et al. teach the first label and the substrate being physically connected (YFP and CFP are attached to the substrate peptide, pg. 15004, Figure 1a), the substrate being a polypeptide (substrate is shown as a peptide, pg. 15004, Fig. 1a) and the enzyme being a protein kinase that phosphorylates serine/threonine and tyrosine (design works for serine/threonine and tyrosine kinases, pg. 15008, left column, second paragraph).

With respect to claims 21 and 29, Ting et al. in view of Burbaum et al. further in view of Walker et al. as applied to claims 1 and 18, teach the limitations of the claim. Ting et al. further teach the polypeptide comprising a second label wherein the first and second labels interact to produce the first signal when the substrate is not phosphorylated and a second signal when the substrate is phosphorylated (pg. 15004, Fig. 1a; pg. 15003, left column, last paragraph-right column, first paragraph).

Regarding claims 23 and 31, Ting et al. teach the first label located at the N-terminus of the polypeptide and the second label located at the C-terminus end of the polypeptide (pg. 15004, Fig. 1a).

With respect to claims 24 and 32, Ting et al. teach the first and second labels being fluorophores capable of exhibiting FRET (pg. 15003, left column, last paragraph-right column, first paragraph).

Regarding claim 25, Ting et al. teach the phosphorylation of the substrate triggers a conformational change in the polypeptide causing a FRET change between the first label and the second label (pg. 15003, left column).

7. Claims 13, 19, 22, 30 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ting et al. (Genetically encoded fluorescent reporters of protein tyrosine kinase activities in living cells, 2001, PNAS, Vol. 98, no. 26, pages 15003-15008) in view of Burbaum et al. (US 5,981,207) further in view of Walker et al. (Signaling pathways underlying eosinophil cell motility revealed by using caged peptides, 1998, PNAS, pg 1568-1573), as applied to claims 1, 21 and 29, and Kris et al. (US 2003/0096232).

Ting et al. in view of Burbaum et al. further in view of Walker et al., teach a composition comprising an enzyme substrate, a first label and a first caging group, but fail to teach the substrate being specific for a protease and the location of the first label on the polypeptide.

Kris et al. teach detection of enzyme activity wherein a substrate is specific for a kinase or a protease (par. 18 and 78), in order to provide a surface that can detect the activity of a plurality of enzymes.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the composition of Ting et al. in view of Burbaum et al. further in view of Walker et al., a protease as the enzyme as taught by Kris et al., in order to identify potential blood thinners or agents which cause blood clots.

Regarding claim 19 and 22, Kris et al. also teach a polypeptide substrate (par. 18-19), wherein the one polypeptide comprises a first label and substrate for kinase (labeled antibodies bind to substrate, and therefore a single polypeptide comprises the substrate and first label, par. 256-258), the substrate comprising a tyrosine residue capable of being phosphorylated by the kinase (par. 256), wherein the first label is located at the tyrosine

residue and exhibits a first signal when the residue is not phosphorylated and the second signal when the signal is phosphorylated (labels bind to phosphorylated substrates, and therefore bind to the phosphorylated residues, par. 258).

With respect to claim 61, Ting et al. teach a kit comprising a substrate and a first label (col. 3, lines 16-23). Burbaum et al., as described above, teach a caging group, and Kris et al. teach including instructions for use in a kit (par. 84-87).

8. Claims 47-56, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ting et al. in view of Burbaum et al. further in view of Walker et al., as applied to claim 1, and Fischer et al. (Cellular Delivery of Impermeable Effector Molecules in the Form of conjugates with Peptides capable of mediating membrane translocation, 2001, Bioconjugate Chemistry, Vol. 12, No. 6, pages 825-841).

Ting et al. in view of Burbaum et al. further in view of Walker et al., teach a sensor comprising one or more molecules, but fail to teach the one or more molecules associated with a cellular delivery module.

Fischer et al. teach delivery polypeptide vectors are used to transport entire proteins into a cell (pg. 827, right column, second paragraph), in order to provide delivery of proteins that are longer than a few peptides into a cell.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the substrate of the composition of Ting et al. in view of Burbaum et al. Walker et al., a cellular delivery module of a polypeptide as taught by Fischer et al., in order to provide efficient preparation for in vivo analysis of enzyme activity.

Regarding claim 49, Fischer et al. teach the cellular delivery module covalently attached to the one or more molecules (pg. 825, abstract).

With respect to claims 52-54, Fischer et al. teach that the cellular delivery module can also be used as a sub cellular delivery module by directing the proteins associated with the module to the same component (pg. 826, right column), in order to provide more accuracy. Fischer et al. teach the sub cellular delivery module being a polypeptide (pg. 827, right column, second paragraph) and covalently attached to the one or more molecules (pg. 825, abstract).

With respect to claims 59 and 60, Fischer et al. teach a polypeptide having an attached oligonucleotide to gain entry into a cell (pg. 827, left column, last paragraph-right column, first paragraph). Although Fischer et al. do not specifically teach a second oligonucleotide bound to a matrix or the specificities of the matrix, the second oligonucleotide and matrix do not structurally limit the caged sensor or the composition and is drawn to a capability. Since the caged sensor taught by Ting in view of Burbaum further in view of Walker and Fischer teach the required structural limitations recited by the claim, the oligonucleotide is capable of binding to a second oligonucleotide that is bound to a bead at a predetermined location within an array.

Regarding claims 50, 51, 55 and 56, Burbaum et al. teach covalently attaching a caging group to a polypeptide in order to control activation of the polypeptide (col. 7, lines 37-47).

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include on the cellular delivery modules, a caging group as taught by Burbaum et al., in order to provide control for the time of introduction of the sensor into cellular components.

Allowable Subject Matter

9. Claims 26-28 and 33-46 are allowable over the prior art for the reasons stated in the office action dated 16 December 2005.

Response to Arguments

10. Applicant's arguments with respect to the pending claims have been considered but are moot in view of the new ground(s) of rejection. The previous rejections of the claims have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the teachings of Ting et al. in view of Burbaum et al. further in view of Walker et al. as described above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melanie Yu whose telephone number is (571) 272-2933. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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